APPENDIX 5

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DOES THE ADMINISTRATION OF DIETHYLSTILBESTROL DURING PREGNANCY HAVE THERAPEUTIC VALUE?*†

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In 1946 Smith and Smith[1] suggested that increasing amounts of diethylstilbestrol should be administered to all women during pregnancy to prevent or decrease the hazards of the late complications of pregnancy for mothers and babies. The basis for such prophylactic therapy as well as the active therapy of these pregnancy complications stems from a series of experiments by the Smiths on the steroid hormones in normal and abnormal pregnancy.[2] These laboratory observations and their theoretical implications were supported by clinical observations, part of which were made under the supervision of the Smiths and, part were the collected reports of other clinical observers.

The use of diethylstilbestrol to prevent and to treat pregnancy complications is based on the supposition that there develops a deficiency in the production of progesterone and other steroids by the placenta which predisposes to or causes these pregnancy complications. The secretion of these steroids can be stimulated by diethylstilbestrol. The increased amounts of steroids made available by the placenta postpone, reduce the severity of, or prevent some of the late complications of pregnancy.

The laboratory experiments which provided the background for this interesting concept of the Smiths have lacked confirmation by other investigators. Davis and Fugo[3, 4] in two reports noted that the administration of diethylstilbestrol to patients during pregnancy did not result in an increased output of urinary pregnanediol, a measure of progesterone metabolism. Sommerville, Marrian and Clayton[5] confirmed these observations and noted a drop in urinary pregnanediol and no gross change in endogenous estrogen. Although many additional experimental data will be necessary to determine the role of diethylstilbestrol in placental steroid metabolism, this paper will confine itself to the clinical implications of the Smith concept.

Smith and Smith in 1949[6] reported on the influence of diethylstilbestrol on the progress and outcome of pregnancy in a series of primigravidas. As

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Since our data were at variance with those of the Smiths, they were all rechecked. The charts of patients with toxemia of pregnancy, premature delivery, stillbirths and neonatal deaths, and any other complication or abnormality, were examined again by one of the senior authors with no knowledge of the kind of medication. There was no significant change in any of the results.

TABLE IX. CONGENITAL ANOMALIES

TYPE OF ANOMALY	PRIMIPARAS		MULTIPARAS	
	STILBESTROL	CONTROL	STILBESTROL	CONTROL
Minor	7	7	9	4
Skin, as papilloma	7	12	7	6
Cystocele, hydrocele	4	3	3	2
Harelip, cleft palate, etc.	1	0	0	1
Clubfoot, multiple digits	2	5	6	2
Mongolism	0	0	0	1
Brain and spinal cord	1	0	0	0
Cardiac, etc.	2	1	1	2
Gastrointestinal	1	0	0	0
Genitourinary	0	2	0	3
Multiple major	2	2	1	1
Total anomalies	27	32	27	24
Total infants	426	415	375	361

Conclusions

A strictly controlled clinical trial of the therapeutic value of diethylstilbestrol administered to patients during pregnancy in reducing the hazards of some of the late complications of pregnancy for mothers and babies has been reported.

The various complications were studied in the total unselected group of patients divided into primigravidas, primiparas, and multiparas. Then the groups were again studied after all groups were corrected to compare with the Smiths'.

The results of the administration of diethylstilbestrol in graduated amounts to 840 patients according to a schedule suggested by the Smiths were compared with the results of an identical placebo trial given to 806 patients. Stilbestrol did not reduce the incidence of abortion, prematurity, or postmaturity. Premature babies of stilbestrol-treated mothers were no longer nor more mature for their gestational ages than comparable prematures in the control group of placebo-treated mothers. It did not decrease the incidence of perinatal mortality. It did not decrease the frequency of the toxemias of pregnancy.

Acknowledgment is made to Eli Lilly and Company for aid in making the stilbestrol and placebo tablets with the dye and for the final determination of the stilbestrol; to Lillian Natusko for the examination of the urines for phenol red; to the staff and residents for their cooperation.

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